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# Is Aspirin Effective in Helping to Prevent Breast Cancer in Women Ages 45 Years and Older?

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**Is aspirin effective in helping to prevent breast cancer in women ages 45 years  
and older?**

Kristen M. Quartuccio, PA-S

A SELECTIVE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not aspirin is effective in helping to prevent breast cancer in women ages 45 years and older.

**STUDY DESIGN:** Review of three English language primary studies published in 2005, 2007, and 2008

**DATA SOURCES:** Two randomized, double blind, placebo controlled clinical trials and one prospective, population based cohort study comparing aspirin to placebo were found using PubMed and Cochrane databases.

**OUTCOMES MEASURED:** Breast cancer development was measured in several ways. Tumor characteristics were measured at diagnosis, including size, metastasis to lymph nodes, histology of the mass, histology differentiation, and estrogen and progesterone status. Outcomes were also measured by pathology reports, cytology reports, on strong clinical and radiologic or laboratory marker evidence, and also self reported questionnaire.

**RESULTS:** The two randomized controlled trials showed that the use of aspirin has no significant effect on the prevention of breast cancer. The cohort study showed an inverse relationship between the use of aspirin and the risk of cancer incidence and mortality.

**CONCLUSIONS:** Although the two RCTs showed no effect of aspirin on the prevention of breast cancer, the cohort study showed some promise in the use of aspirin and breast cancer prevention. The dose of aspirin used in the RCTs was only 100mg, and the doses in the cohort study varied based on individual reporting. Increasing the dose of aspirin to 325mg in future studies may show some effect in the prevention of breast cancer.

**KEY WORDS:** Aspirin, Breast Cancer

## INTRODUCTION

Breast cancer is defined as “a malignant proliferation of epithelial cells lining the ducts or lobules of the breast”, resulting from a single cell that undergoes acquired or germ-line mutations, and eventually expresses “full malignant potential”.<sup>1</sup> After skin cancer, breast cancer is the most commonly diagnosed cancer in U.S. women, with death rates higher than for any other cancer, besides lung cancer. Mortality has decreased slightly due to early detection methods; however prevention of the disorder could further lower mortality. One in eight women in the United States will develop breast cancer during her lifetime. About 85% of breast cancer cases occur in women with no prior family history of breast cancer. In 2011, “230,480 new cases of invasive breast cancer were expected to be diagnosed in women in the U.S.”, with “57,650 new cases of non-invasive (in situ) breast cancer”, and “39,520 women in the U.S. were expected to die in 2011 from breast cancer”.<sup>2</sup> The national expenditure for breast cancer care in 2006 was \$13.886 billion.<sup>3</sup>

The biggest risk factor for the “development of breast cancer is age”, with the median age of diagnosis of 61 years, though many women with breast cancer do not have any “identifiable risk factors”.<sup>4</sup> The initial discovery of breast cancer in about 70% of patients is a lump in the breast that is “single, non-tender” and “firm to hard with ill-defined margins”.<sup>4</sup> Mammography is useful in that it detects masses before they can be palpated, sometimes even 2 years prior to being felt in the case of slow growing cancers. The most common method of treating breast cancer is surgical resection which can be breast conserving or a full mastectomy. Other treatment methods include chemotherapy, radiation therapy and hormone therapy such as ERDs, SERMs and aromatase inhibitors.<sup>4</sup>

Evidence has shown that aspirin might be effective in the prevention of breast cancer, so that women will not have to undergo such invasive measures to treat breast cancer in the future. NSAIDS have been shown to “suppress tumor growth” in “experimental animal models”<sup>5</sup>. Observational epidemiological studies have suggested a strong inverse association, with risk reduction 20-50% for various sites in several different cancer types, including breast cancer. Aspirin is thought to reduce cancer risk through its effect on cyclooxygenase (COX). Aspirin inhibits COX enzymes, particularly COX 2 which is “linked to inflammation and tumor growth”, effecting “apoptosis, cell migration and angiogenesis”<sup>5</sup>. There is also a possible role of aspirin as an antioxidant and in the “modulation of estrogen biosynthesis”.<sup>5</sup>

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not aspirin is effective in helping to prevent breast cancer in women ages 45 years and older.

## **METHODS**

The criteria for selection of studies included women ages 45 years and older. The intervention used was aspirin use. The types of studies included consist of two randomized control trials (RCT) and a prospective, population based cohort study. In each RCT, results are compared between the groups taking aspirin and the placebo group. The cohort study compares groups taking aspirin to those not taking medication<sup>6</sup>. The outcomes measured are breast cancer incidence and mortality.

Articles were found via Pubmed and Cochrane. The key words used in searches were “aspirin” and “breast cancer”. All articles are written in English and were published in peer reviewed journals. Articles were selected based on their relevance and on the importance of outcomes of the patient or POEMs. Inclusion criteria consisted of articles using aspirin as an

intervention, female participants aged 45 years and older, and studies that were randomized controlled trials. Exclusion included any observational studies prior to 2005 because of an already existing non-Cochrane meta-analysis. The statistics reported of use include Relative Risk (RR), 95% Confidence Interval (CI), Relative Risk Reduction (RRR), Absolute Risk Reduction (ARR), Numbers Need to Treat (NNT), and p-value. Table 1 includes the demographics of the included studies.

**Table 1: Table of Demographics and Characteristics of included studies**

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Bardia, 2007 <sup>6</sup>	Prospective, population based cohort study	22507	55-69	Postmenopausal women	Premenopausal, cancer other than nonmelanoma cancer, receiving chemotherapy through 1992, history of heart disease through 1992, died between 1986 and 1992, did not complete 1992 questionnaire	0	Self reported aspirin or NSAID intake
Cook, 2005 <sup>5</sup>	RCT	39,876	45 years and older	No history of cancer or cardiovascular disease or other major chronic illness	History of adverse effects to aspirin; taking aspirin or NSAIDs more than once a week; taking anticoagulants or corticosteroids; taking vitamin A, vitamin E or beta carotene more than once a week	0	Low dose aspirin, 100 mg administered every other day for 10 years
Zhang, 2008 <sup>7</sup>	Double blind, RCT	39,876	45 years and older	No history of cancer or cardiovascular disease or other major chronic illness	History of adverse effects to aspirin; taking aspirin or NSAIDs more than once a week; taking anticoagulants or corticosteroids; taking vitamin A, vitamin E or beta carotene more than once a week	0	Low dose aspirin, 100 mg administered every other day for 10 years

## OUTCOMES MEASURED

All outcomes measured were based on relevance to Patient Oriented Evidence that Matters (POEMS). Zhang et. al. measured outcomes based on “tumor characteristics at diagnosis”, including size, metastasis to lymph nodes, histology of the mass, histologic differentiation, estrogen and progesterone receptor status<sup>7</sup>. Cook et. al. measured outcomes based on pathology reports, cytology reports and on “strong clinical and radiological or laboratory marker evidence”<sup>5</sup>. For reported cases of breast cancer, medical records and other relevant information was sought and reviewed by physicians blinded to the treatment<sup>5</sup>. Lastly Bardia et. al. measured outcomes based on self reported questionnaire, with cancer incidence and mortality ascertained by annual linkage to the “Iowa Surveillance, Epidemiology and End Results Cancer Registry and death certificates”<sup>6</sup>.

## RESULTS

Bardia et. al. determined the effects of aspirin on breast cancer through a prospective, population based cohort study, in which participants were analyzed via their returned questionnaires. The study found that during 10 years of follow up, “3487 cases of cancer were observed”, with an “inverse trend for cancer risk with frequency of aspirin use ( $P_{\text{trend}} < 0.001$ )” observed<sup>6</sup>. The use of aspirin was inversely associated with cancer incidence, as seen in table 2.

**Table 2: Relative Risk and 95% Confidence Interval for Incidence of Breast Cancer in Those Taking Aspirin**

Bardia et. al. 2007		
Aspirin Use per week	RR	95% CI
Never	1.00	Referent
Ever	0.84	0.80 to 0.93
≤1	0.85	0.70 to 0.93
2-5	0.83	0.77 to 0.94
≥6	0.81	0.80 to 0.98



Bardia et. al. found a “weak inverse association between the frequency of aspirin use and cancer mortality”, with aspirin ever use “inversely associated with cancer mortality (RR = 0.87, 95% CI = 0.76 to 0.99)”, as seen in table 3.<sup>6</sup>

**Table 3: 95% Confidence Interval for Incidence and Mortality of Breast Cancer in Those Taking Aspirin**

Bardia et. al. 2007		
Aspirin Use per week	RR	95% CI
Never	1.00	Referent
Ever	0.87	0.76 to 0.99
≤1	0.91	0.78 to 1.06
2-5	0.83	0.69 to 1.00
≥6	0.82	0.68 to 0.99

Bardia et. al. excluded women who were premenopausal, had cancer or who were receiving chemotherapy since these groups would alter the incidence of breast cancer and would make it difficult to determine if aspirin had an effect. The study observed differences in smokers versus nonsmokers. The “inverse association between aspirin use and breast cancer mortality was evident among never smokers (for aspirin use six or more times per week versus never use, 95% CI = 0.61 to 0.99) and suggestive among former smokers (for aspirin use six or more times per week versus never use, 95% CI = 0.51 to 1.24) but not among current smokers (for aspirin use six or more times per week versus never use, 95% CI = 0.63 to 1.46)”<sup>6</sup>. The study also looked at the effect of NSAIDs and the risk of cardiovascular incidences with both aspirin and NSAIDs.

Zhang et. al. looked at cases of total, invasive and in situ breast cancer, finding no significant effect on risk with low dose aspirin according to tumor size, histology and estrogen or progesterone receptor status. Total cases of breast cancer with aspirin treatment was “762 cases”, while the total cases with placebo treatment was “779 cases”, with a “95% CI of 0.88 – 1.08”<sup>7</sup>. Cases of in situ breast cancer with aspirin treatment was “159 cases”, while the cases of in situ

cancer with placebo treatment was “165 cases”, with a “95% CI of 0.78 to 1.20”<sup>7</sup>. Cases of invasive breast cancer with aspirin treatment was “608 cases”, while the cases of invasive cancer with placebo treatment was “622 cases”, with a “95% CI of 0.87 to 1.09” as seen in table 4<sup>7</sup>. “Morbidity and mortality follow-up were 97.2% and 99.4%” respectively (deaths were reported by “family members, postal authorities, and a search of the National Death Index”) <sup>7</sup>. The number needed to treat (NNT) was -1429, meaning that for every 1429 participants who took prophylactic aspirin, there was one fewer incidence of breast cancer than in the group of participants taking placebo.

**Table 4: Cases of Breast Cancer According to Randomized Aspirin Treatment**

Zhang et. al. 2008				
	Number of cases with Aspirin (n=19934)	Number of cases with placebo (n=19942)	Hazards Ratio	95% CI
Total Breast Cancer	762	779	0.98	0.88 – 1.08
In situ Breast cancer	159	165	0.96	0.78 - 1.20
Invasive Breast cancer	608	622	0.98	0.87- 1.09

Cook et. al. found after 10 years of follow up, there were “1230” cases of invasive breast cancer, with “1535” cases of in situ breast cancer<sup>5</sup>. There was no effect of aspirin on the incidence of breast cancer with the “95% CI of 0.87 to 1.09 and p= 0.68”<sup>5</sup>. Table 5 shows that there is no increase in the effect of aspirin over duration of time.

**Table 5: Cumulative Effect of Aspirin on Breast Cancer Prevention over Time**

Cook et. al. 2005		
Follow up time	95% CI	P
2 years	0.87 – 1.09	0.74
5 years	0.83 – 1.12	0.63

Cook et. al. also compared the incidence of breast cancer in smokers and nonsmokers. “Among never smokers, women assigned to aspirin had an increased risk (95% CI = 0.94 – 1.30,

p=0.21), but among past smokers they had a decreased risk (95% CI = 0.94 – 1.30, p=0.07), with no effect among current smokers (95% CI = 0.69-1.25, p= 0.63)”<sup>5</sup>. The study took into account compliance of participants as well. There were no effects on breast cancer in women at the time they stopped taking “at least two thirds of their study pills”<sup>5</sup>. “Among women who consistently took at least two thirds of their study aspirin or placebo during the first 2 years”, there was no effect on breast cancers occurring after 2 years of follow up “(95% CI = 0.87 – 1.13 and p = 0.88)”, and “the same was true among women who complied with study medication use during the first 5 years of intervention”<sup>5</sup>. The study also looked into the effect of aspirin on several other types of cancers. The NNT in this RCT was -1429.

## DISCUSSION

The two RCTs used aspirin at dosages of 100 mg every other day while the prospective cohort study asked participants to report only how regularly they took aspirin and not the amount. Taking higher doses of aspirin more regularly might provide some benefits.

Aspirin is widely available and convenient for patients in that it is over the counter. Contraindications to use include hypersensitivity to salicylates or other NSAIDs, asthma, rhinitis, nasal polyps, inherited or acquired bleeding disorders or pregnancy. Adverse effects include salicylate sensitivity, tinnitus, and upper gastrointestinal events.<sup>8</sup>

Limitations existed in the articles included in this paper. In all of the studies, patients were responsible for taking medication and reporting how compliant they were. The studies were not performed in in-patient settings where they could be monitored because they persisted for a decade. There is some variability in the results in that some patients might not have been accurate in recording how much medication they took. The cohort study was not performed as a

double blind RCT, but instead participants filled out questionnaires about the medications they took and how often.

There were limitations in searching for articles as well. There are an abundance of cohort studies but few RCTs on the topic at hand. RCTs are more useful in that they typically perform studies in a double blind fashion, which eliminates bias.

## **CONCLUSION**

According to the two RCTs, aspirin is not effective in preventing breast cancer in women ages 45 years and older. The prospective cohort study however did show aspirin to be effective in preventing breast cancer in women ages 45 years and older. The issue at hand comes down to dosage. Participants who received aspirin in the RCTs took 100mg every other day of aspirin. In the cohort study, participants recorded how often they took aspirin, which could have ranged in value with some even taking 325mg (the study does not state the amounts). Cook et. al. states that low dose aspirin appears “relatively specific for COX-1”, though “higher doses inhibit both COX-1 and COX-2 and may have a stronger anti-inflammatory effect”<sup>5</sup>. “COX-2 expression” is “increased in breast cancer tumor tissue”, which suggests that “higher doses of aspirin may be more effective in cancer prevention”<sup>5</sup>.

Future study is warranted to determine if higher dosages of aspirin at closer intervals is more effective than 100 mg of aspirin every other day<sup>7</sup>. The most effective way to determine this is by a double blind RCT comparing the higher and lower dosages of aspirin against a placebo.

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